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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,809	07/03/2001	Raghavan Rajagopalan	MRD/63	5120

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David E. Jefferies
Wood, Herron & Evans, L.L.P.
2700 Carew Tower
441 Vine Street
Cincinnati, OH 45202-2917

EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	PAPER NUMBER
1624	5

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,809	RAJAGOPALAN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *3-10 and 15-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11-14 and 23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an application filed on 9/5/02. There are thirty claims pending and fourteen under consideration. Claims 1, 2, and 11 are compound claims. Claims 12-14 and 23-30 are use claims. This is the first action on the merits. The application concerns some thiadicarbocyanine compounds and uses thereof.

Election/Restrictions

2. Applicant's election with traverse of Group I, the cyanine compounds in Paper No. 4 is acknowledged. The traversal is on the ground(s) that no restriction within a claim may be made. Applicants cite In *re Weber* 198 USPQ 331 in support of their position. This is not found persuasive because Applicants argue that such a restriction requirement amounts to a rejection. This is not found persuasive because the case cited by Applicants deals with a rejection of claims under 35 USC 121 and not on the ability of the USPTO to restrict an application. Paragraph §803.02 of the MPEP lists the procedure to follow when Markush-type claims, like Applicants, are restricted. Since a Markush claim is a single claim, the USPTO clearly has the ability to restrict within a claim. In addition, although the Applicants are not filing under Rule 371, the MPEP states in Rule 475, "determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions

are claimed in separate claims or as alternatives within a single claim". Furthermore, there exists no substantial common structural feature in claim 1 such that it may be alleged such a structural feature is primarily responsible for the pharmacological activity observed by the Applicants. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 3-10 and 15-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 4.

Specification

4. The disclosure is objected to because of the following informalities: in lines 21-22, page 9 Applicants describe the formula of Figure 2 as "a cyanine derivative". The issue of what a cyanine dye is or is not is discussed in detail below. Appropriate correction is required.

Abstract

5. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the

compound or composition should be given as well as its use. The abstract is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Title

6. The title of the invention is not descriptive after the restriction. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: replacing the word "Dye" with "Cyanine" or "Thiadicarbocyanine".

Priority

7. The status of all nonprovisional parent applications referenced should be included. Application 09/484,322 has issued as US Patent No. 6,395,257 on 05/28/2002.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 11-14, 23-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "comprising" in claim 1 is an open term. What additional structural elements beyond the formula given in claim 1 are being claimed? The Examiner suggests removing the word and using "sufenate compound"

9. Claims 1, 2, 11-14, 23-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" are all indefinite for two reasons. "E" cannot be a molecule, which lacks any free valence, it must be a univalent radical.

10. Secondly, what are the chemical structures of these fragments that define radical "E"? These are not art-recognized terms. The passage spanning line 17, page 12 to line 12, page 13 lists the function that these radicals are to perform, but does not clarify the molecular structures. Applicants' statement that "E" is an epitope only further clouds the issue. The Examiner understands that an epitope is a portion of a protein chain in an antibody. Is "E" an antibody or only a short peptide segment from an antibody? Are the synthetic biomolecules listed in lines 11-13, page 13 "E"?

11. Claims 1, 2, 11-14, 23-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specific phrase "carbohydrate receptor binding molecule" is indefinite. There is an entire class of such carbohydrate receptors, quite possibly thousands, and generally

poorly understood and characterized. How would one know if any molecule E bound to such a receptor without checking all such receptors?

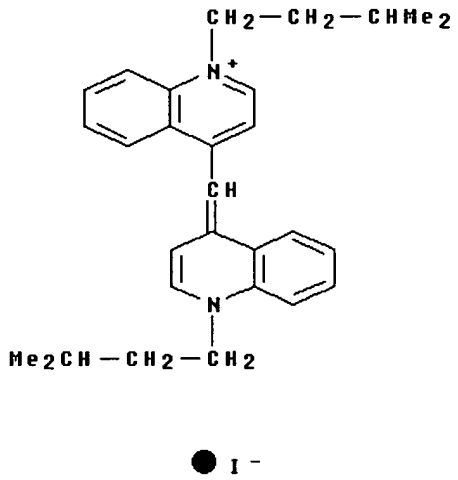
12. What does "associated with biomolecules" mean in claim 11 in Applicants definition of "E". Are Applicants' claiming these substances, or antibodies to these? Must "E" be a peptide segment of an antibody or can it be a hormone, amino acid etc?

13. Claim 11 recites the limitation "associated with ... monoclonal antibodies, polyclonal antibodies, receptors [and] receptor binding molecules" in lines 5 and 6. There is no antecedent basis for this limitation in the parent claim 1, which lists seven specific receptors, not all receptors or all molecules that bind to any receptor. This would require testing all antibodies to every antigen to determine what is included by this claim

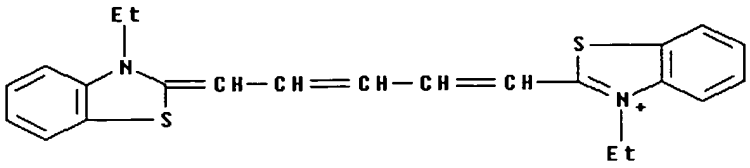
14. Claims 1, 2, 11-14, 23-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "radical derived from ... cyanines" is indefinite for two reasons. Firstly, the verb "derived" is, in essence, a product by process claim. Yet, Applicants have not described the intended processes sufficiently that we may understand the structures of the compounds they claim. Webster's New World Dictionary defines derivative as "a substance derived from ... another substance by chemical change", and

"substitution of one or more elements or radicals for one or more constituents of the original substance" has occurred. All implying that new chemical bonds have formed. The question is, what compounds falling outside the structural limitations of cyanines are covered under the rubric of derivatives.

15. Secondly, cyanine is a specific compound with registry number [532-42-2] and shown below. It is a di-quinoline compound. Hawley (Condensed Chemical



Dictonary) defines cyanine dye as "consisting of two heterocyclic groups (usually quinoline nuclei) connected by a chain of conjugated double bonds containing an odd number of carbon atoms." Applicants' Figure 2 contains a bis benzothiazole. Substructure search of Applicants structure in Chemical Abstracts discloses a number of compounds including 3-ethyl-2-[5-(3-ethyl-2(3H)-benzothiazolylidene)-1,3-pentadienyl]-benzothiazolium, iodide whose structure is also shown below.



I⁻

Among the trivial names for this bis benzothiazole are diethylthiadicarbocyanine and [2-bis(3-ethylbenzothiazolyl)]pentamethine cyanine. Applicants seperately listed indocyanines and phthalocyanines in their orginal claim, implying that not all dyes containing the word cyanine in their name are "cyanines". There are differences in the art as to the meaning of "cyanine". When we look to the specification to see what Applicants may have meant by the use of this term, we find the single example of a thiadicarbocyanine. Are the quinolines covered? Are there any limitations as to the heteroaryl ring? *In re Sus*, 306 F.2d 494, 504, 134 USPQ 301. The Examiner has searched the bis benzothiazole compounds only.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 11-14, 23-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for radical "E" being

dihydroxyindolecarboxylic acid or the peptide Cytate, does not reasonably provide enablement for all the other offered E binding molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. If E is an epitope from an antibody, raising all possible antibodies to the somatostatin receptor and locating all the possible epitope sites on these antibodies is an impossible task. Alternatively, screening all "hormones, amino acids, peptides, ... and aptamers" to determine if they bind to the receptors listed in claim 1 is an open-ended and potentially inconclusive research project.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

Locating the epitope on any particular antibody somatostatin receptor say, would a moderate degree of experimentation. However, all possible antibodies would have to be made because the individual epitope sites would differ. The

direction concerning the compounds claimed is found in Figure 2. In that figure, the radical "E" is described as "Biomolecule". Thus, Figure 2 does not appear to be a working example. There are no working examples of a compound of formula given in claim 1. There is no procedure given to determine the affinity of any substance to the receptors listed in claim 1. The state of the art for tumor binding agents is given in the references spanning line 22, page 13 to line 5, page 14. The artisan using Applicants invention would be a medicinal chemist Ph. D. degree in chemistry and several years experience making bioconjugates. The predictability in art of preparing antibodies is low. The absence of working examples and the absence of any of the above references teaching the determination of any epitope implies that predictability is small. Reference AR teaches the use of an octapeptide which binds to the somatostatin receptor. A radical which derived from this peptide would fit the definition of "E" but is unclear if there additional such peptides or how the peptide Cytate was identified. The scope of the claimed subjected matter, as far as the "E" radical, is large.

17. Claims 1, 2, 11-14, 23-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The

issue concerning the meaning of phrases "somatostatin binding molecule" ... "carbohydrate binding molecule" *etc* are discussed above.

According to the MPEP §2163 I. A. "the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The MPEP states in §2163 II. 3. ii) "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at

1406." Applicants have disclosed no species and have made no assertion that there is any correlation between the function of radical "E" and its structure.

18. Claims 1, 2, 11-14, 23-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The issue concerning the meaning of "cyanine" is discussed above, as is the rational for the lack of understanding of the skilled medicinal chemist of a critical feature of formula in claim 1.

19. Claims 12-14 and 23-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific diseases listed in the specification, does not reasonably provide enablement for treating every "target tissue". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification does not set forth any steps involved in determining how to identify "a target tissue". It is unclear what diseases and treatments applicant is intending to encompass. In which diseases do these targets exist? Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With

out such clinical research to identify the tissues and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

In lines 14-16, page 2, line 18, page 2, and the lines spanning line 22, page 2 to line 2, page 3 Applicants discuss specific diseases amenable to photo therapy. The Examiner suggests claiming treatment of these specific diseases.

Conclusion

20. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
October 31, 2002